IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S) :	Mueller-Walz, et al.	CONFIRMATION. NO.:	5874
SERIAL NUMBER :	10/574,334	EXAMINER :	Kennedy, Nicoletta
FILING DATE :	March 7, 2007	ART UNIT :	1611
FOR :	AEROSOL FORMULATIONS COMPRISING FORMOTEROL FUMARATE DIHYDRATE		

Via EFS

DECLARATION UNDER 37 C.F.R. § 1.132

I, Rudi Mueller-Walz, Ph.D., declare:

1. I am currently Head of Inhalation Formulation and Process Development at SkyePharma, A.G. In this position I am responsible for development of inhaled dosage forms and device development. My *curriculum vitae* is already of record in this case.

2. This Declaration is made to address the difficulties of substituting a steroid in suspension with a steroid in solution in an aerosol suspension formulation of FFDH.

3. Having one active drug of the combination drug product suspended and the other active (the steroid in this case) dissolved or solubilized is a very delicate and unusual concept. In order to dissolve a sufficient amount of the second active to achieve the effective dose for treatment, it is necessary to add a co-solvent to the hydrofluoroalkane propellants (HFAs) due to the very limited solvent strength of the HFAs.

4. Ethanol is typically used as a co-solvent in aerosol formulations. The amount of ethanol used depends on the characteristics of active and the required dose for delivery. However, the use of ethanol as a co-solvent in HFA suspension formulations presents additional formulation problems that make its successful use challenging and unpredictable. For example, if the amount of ethanol required to achieve dissolution of the second active in amounts sufficient to achieve the required delivered dose is too high, it could result in the dissolution of small amounts of the first active, the suspended drug component, in the ethanol phase. If this happens, the formulation will not be stable due to a physical phenomenon referred to as 'Ostwald ripening'. In this situation, the smaller particles (crystals) of the suspended active would constantly loose mass due to their higher surface energy and dissolve in the ethanol phase while the bigger particles would grow in mass by binding the dissolved molecules into their

crystal lattice. As a result, the suspended drug particles will become ever bigger, the particle size distribution of the suspended drug will shift towards the larger side of the spectrum and the fine particle dose (*i.e.*, the inhalable part of the delivered dose of the aerosol) will decrease drastically. In addition, higher amounts of ethanol may be also impact the chemical stability of the dissolved drug (the steroid). Such a formulation is hence very challenging and seldom achieved due to the conflicting requirements of the two actives as described herein.

5. As a person signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Declarant's Signature

14/Dec/2011
Date

Full Name of Declarant: Rudi Mueller-Walz, Ph.D.